Ref. (18)

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KITASATO KENKYUSHO SH *JP 07224067-A
94.02.15 94JP-018612 *(95.08.22)* C07D 498/22 // A61K 31/52, 31/55 (C07D 209:00, 309:14, 498/22, 273:06) (C07D 209:00, 273:06, 498/22, 309:28) (C07D 209:00, 307:24, 498/22) (C07D 209:00, 309:10, 498/22, 273:06)

7-Alkoxy- or hydroxy-staurosporine deriv. prepn. in high yield - from corresp. 7-unsubstituted cpd., alcohol and quinone oxidant, used as protein kinase C inhibitor

C95-144522
Addnl. Data: ASAHI KASEI KOGYO KK (ASAH)

B(6-E5, 14-D6) .2

Prepn. of a 7-alkoxy-staurosporine deriv. (I) contg. a substd. tetrahydropyran or tetrahydrofuran ring comprises reacting the corresp. 7-unsubstituted staurosporine (II) with a lower alcohol in the presence of a quinone oxidant in an inert solvent.

The obtd. (I) is opt. hydrolysed in presence of acid catalyst to give the corresp. 7-hydroxy-staurosporine deriv. (I') contg. a substd. tetrahydropyran or tetrahydrofuran ring.

USE

(I) and (I') have various biological activities based on protein kinase C inhibition.

ADVANTAGE

The method gives a high yield without using heavy metal oxidants (such as lead tetraacetate), and is industrially applicable.

OXIDANT

2,3-Dichloro-5,6-dicyano- p-benzoquinone (DDQ), chloranil or o-chloranil is pref. used as oxidant.

REACTION CONDITIONS

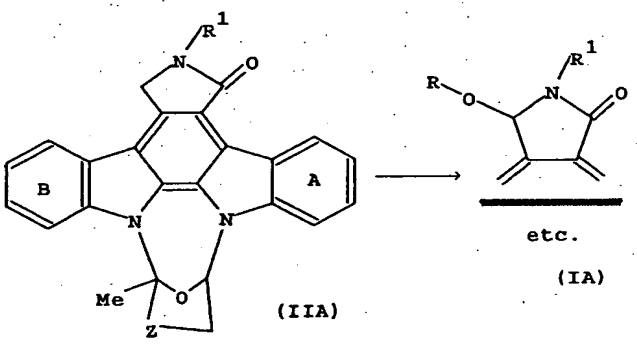
(I) is obtd. by treating (II) with 1-1.2 molar excess of the oxidant and 10-20 molar excess of 1-4C alcohol (e.g. MeOH) at 10-30°C for 2-10 hrs.

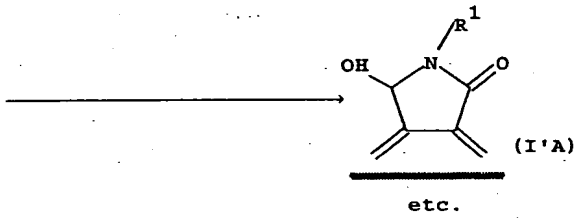
(I') is obtd. from (I) by acid hydrolysis in a mixt. of water and a water-miscible organic solvent (pref. dimethylformamide, N,N-dimethylacetamide or 1,3-dimethyl-2- imidazolinone), in the presence of strong inorganic or sulphonic acid at 40-70°C for 2-10 hrs.

JP 07224067-A+

PROCESS

Reaction is typically as follows:





rings A and B are opt. substd.;
R^1 = H or lower alkyl;
Z = opt. substd. methylene or ethylene, e.g. -C(OH)(COOMe)- or -CH(OMe)-CH(NHMe)-;
R = 1-4C alkyl.

EXAMPLE

A soln. of 944 mg of 4'-N-(2,2,2-trichloroethoxy carbonyl) staurosporine in 10 ml dichloromethane was treated with 1 ml MeOH and 410 mg of DDQ at room temp. for 5 hours. The prod. was taken

JP 07224067-A+/1

up in EtOAc. The organic layer was washed with satd. aq. $NaHCO_3$, dried and evaporated to give a 7-methoxy deriv. in 96% yield.

A soln. of 14.7g of the prod. in a mixt. of 495 ml of DMF and 49.5 ml of 1N HCl was heated at 60-65°C for 3.5 hrs., then treated with 300 ml of 3% aq. ammonia. The pptd. crystals were filtered off vacuum-dried and subjected to silica gel column chromatography using $CHCl_3$ - MeOH - 25% ammonia (99:1:0.1) as eluent to give the 7-hydroxy deriv. in 85% yield. (RMH)
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JP 07224067-A/2